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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,682	05/09/2006	Yohei Okada	03327.2346	3661

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FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER LLP
901 NEW YORK AVENUE, NW
WASHINGTON, DC 20001-4413

EXAMINER	
EBRAHIM, NABILA G	

ART UNIT	PAPER NUMBER
1618	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,682	OKADA ET AL.	
	Examiner	Art Unit	
	NABILA G. EBRAHIM	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 8+13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/28/2008 has been entered.

Status of Claims

Claims 1-4 and 8-13 are pending in the application.

Claim 1 has been amended.

Status of Office Action: Non-Final.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In view of Applicant's arguments, the rejection of claims 1-4, and 8-13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is hereby withdrawn..

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

In view of the amendment to claim 1, the rejection of claims 1, 3-4, and 8-12 under 35 U.S.C. 102(b) as being anticipated by Brann et al. US 6528529 is hereby withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 and 8-13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Brann et al. US 6528529 (hereinafter Brann) in view of any of M. Suzuki et al. Effects of (-)-S-2,8-dimethyl-3-methylene-1-oxa-8-azaspiro[4,5]decane L- tartrate monohydrate (YM796), a novel muscarinic agonist, on disturbance of passive avoidance learning behavior in drug-treated and senescence-accelerated mice, Volume 275, Issue 2, pp. 728-736, 11/01/1995 (hereinafter Suzuki), or Tsukamoto Shin-Ichi WO 9220683 (hereinafter "Shin") and in view of Sako et al. US 6699503 (Sako) and further in view of Takafumi et al. "Prediction of in Vivo Nonlinear First-Pass Hepatic Metabolism of UM 796 from in Vitro Metabolic Data" Vol. 286, Issue 1, 122-127, July 1998 (hereinafter Takafumi).

Brann teaches compounds with activity on muscarinic receptors. Brann's compounds are the same as the instant application recitation (col. 9, lines 4-6) and discloses that the preparation can be sustained-release (col. 12, lines 61+) and that the unit dosage forms can be

in the form of tablets, pills, capsules, powders, granules, elixirs, tinctures, syrups and emulsions, sterile parenteral solutions or suspensions, aerosol or liquid sprays, drops, ampoules, auto-injector devices or suppositories. Note that all these forms usually include carriers.

Brann is deficient in the sense that he did not disclose the tartrate salt of the compound.

Shin teaches the compound (-)-(S)-2,8-Dimethyl-3-methylene-1-oxa-8-azaspiro[4,5]decane L-tartrate having a storage stability superior to that of other salts and being applicable as a medicine (abstract) and also has a selective affinity for the muscarinic acetylcholine receptor. The hydrochloride, fumarate, maleate and di-p-toluoyl-D-tartrate salts of the compound can be utilized in the treatment of diseases. Note that the "treatment of tear and salivary fluid drying" is the intent of use of the composition, which is not considered of weight in the patentability of the instant claims because the prior art composition would have been inherently able to achieve the same use with success. However, it is also noted that it is within the muscarinic agonist effect of the compound to enhance the secretion of lacrimal and salivary glands.

As the title of the reference shows, Suzuki teaches the effects of the compound taught in the instant claims. The reference discloses that the compound is a novel muscarinic agonist, and has an effect on disturbance of passive avoidance learning behavior in drug-treated and senescence-accelerated mice. Muscarinic action of the autonomic nervous system is well known to people skilled in the art (see the attached document that describes the muscarinic activity of the autonomic nervous system, page 3). One of these activities is having anti-drying effect on eyes and the mouth.

Note that the effects of the drug and its mechanism of action recited in claims 3, and 4 are inherent properties of the drug.

Suzuki and Shin disclosed the use of the L-tartrate required by instant claim 2.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce 2,8-dimethyl-3-methylene-1-oxa-8-azaspiro[4,5]decane in a sustained-release form to prolong the action of the compound on lacrimal and salivary glands as disclosed by Brann and produce its tartrate salt because Shin discloses that the L-tartrate has a superior storage stability (abstract).

None of the references teach the use of polyethylene oxide as a polymer for the sustained release formulation.

Sako teaches an invention provides a hydrogel-type sustained-release preparation capable of satisfactorily releasing a drug. The preparation comprising (1) at least one drug, (2) an additive which insures a penetration of water into the core of the preparation and (3) a hydrogen-forming polymer. The formulation provides a steady sustained release effect (abstract). Sako teaches that among hydrogel polymers that are used in sustained-release polymers is polyethylene oxide (PEO) and describes molecular weights and viscosity of the polymer (col. 4, lines 59+ bridging to col. 5, lines 1+). Sako discloses different polymers, however, the reference teaches that the preferred polymer is a PEO and the reference also show how to control the release in a specific time and gives an example disclosing that a release if more than 12 hours, is required, a polymer having a higher molecular weight, preferably an average molecular weight of not less than $2x10^6$ or a higher viscosity, preferably a viscosity of not less than 3000 cps at a concentration of 1% in water at 25°C., is preferable (col. 5, lines 21-28).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine Sako's disclosure of polyethylene oxide preferred use in sustained-release formulations to the combination of Brann and Suzuki or Shin to produce a sustained release formulation comprising 2,8-dimethyl-3-methylene-1-oxa-8-

azaspiro[4,5]decane and adjust the molecular weight according to amount of release needed for the patients and to prolong the action of the compound on lacrimal and salivary glands, the motivation would be the disclosure of Sako that PEO is the preferred polymer to achieve these results. The skilled artisan would have excellent expectation of having a pharmaceutical composition for the treatment of tear and salivary fluid drying.

Regarding the amendments to claim 1 It is noted that the concentration of a drug in the plasma is proportional to the dosage provided to achieve a specific function (in this case, increasing tear and saliva), however, it is noted that Brann teaches that the dosage regimen utilizing the compounds of the invention is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound employed. A physician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the disease or disorder which is being treated. Nevertheless, none of the references teaches literally the maximum plasma concentration.

Takafumi teaches the in vivo metabolic clearance of YM796 (the instant compound). Figure 3 shows that dosages between 40- 50 mg/body reaches plasma concentration of about 150 ng/ml while a dosage of 60 mg/body reaches over this value. Since Brann teaches dosage forms containing between 0.1 to 50.0 mg. Thus Brann discloses a maximum plasma concentration of 150 ng/ml or less. Accordingly, since the person of ordinary skill in the art can adjust the daily dose, and consequently the plasma concentration, it would be obvious to the person of ordinary skill to decide the ratio between the maximum and minimum concentrations of the active ingredient in plasma which both depends on the minimum and maximum doses decided for a patient according to the factors disclosed by Brann.

Response to Arguments

1. Applicant's arguments filed 4/28/2008 have been fully considered but they are not persuasive. Applicant argues that:

- Several parameters can affect the release rate of a sustained release preparation. For example, the release rate can be adjusted by changing the blending ratio of the hydrophilic base and the hydrogel-forming high molecular weight substance; by adjusting the amount of semipermeable membrane used to coat the composition, adjusting the amount of osmopolymer in the push layer of the composition, and adjusting the molecular weight of the hydrophilic polymer in the sustained release composition. See specification page 32, lines 11-17; page 36, lines 16-20; page 40, lines 11-14. In addition to modulating the chemical composition of the sustained release formulation, one can also adjust the physical structure of the formulation by having introducing layers into the formulation, each layer having a different role in delivery of the drug to the recipient. See page 39, line 16 to page 40, line 14. These layers can be changed to thicknesses and shapes to further modulate release rates. See page 41, line 24 to page 42, line 8. Given the factors that can affect the release rate of a drug from a sustained release formulation, Brann's isolated teaching of PEG and polyvinyl pyrrolidone falls very short of constituting a teaching of a sustained release formulation with the specific drug release rate recited in claim 1. Just because these chemicals may be contemplated for use in Brann's compositions does not mean that they will automatically result in the claimed release rates. Thus, the Examiner's assumption is incorrect.

To respond: all Applicant's explanation for the parameters that can affect the release rate are not recited in the claims and cannot be considered as limiting to the scope of the invention. Brann teaches compounds with activity on muscarinic receptors which are the same as the instant application recitation (col. 9, lines 4-6) and discloses that the preparation can be

sustained-release (col. 12, lines 61+) which comprises polyethylene glycol and PVP. Sako teaches the use of Polyethylene oxide. These references read on the instant claims as written.

- The combination of Brann, Suzuki, Shin, and Sako, at best may make it obvious to try using (-) - (S) -2,8-dimethyl-3-methylene-l-oxa-8-azaspiro[4.5]decane in the sustained release formulations taught in Sako. However, as MPEP § 2143 instructs, obvious to try can form the foundation for an obviousness rejection only under limited circumstances in which the Examiner must demonstrate 4 elements.

To respond: The Examiner has not rejected the instant claims based on "obvious to try". Brann teaches compounds with activity on muscarinic receptors. Brann's compound are the same as the instant application recitation and discloses that the preparation can be sustained-release, Shin teaches the tartrate salt of the compound, Suzuki teaches the effect of the recited compound on the lacrimal and salivary glands and finally, Sako teaches the use of polyethylene oxide to achieve sustained release of a drug. As the office action shows there was a motivation in combining Brann, Suzuki, and shin as follows: it would have been obvious to one of ordinary skill in the art at the time the invention was made to produce 2,8-dimethyl-3-methylene-1-oxa-8-azaspiro[4,5]decane in a sustained-release form to prolong the action of the compound on lacrimal and salivary glands as disclosed by Brann and produce its tartrate salt because Shin discloses that the L-tartrate has a superior storage stability (abstract). Further to rely on Sako, there was motivation as follows: it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine Sako's disclosure of polyethylene oxide preferred use in sustained-release formulations to the combination of Brann and Suzuki or Shin to produce a sustained release formulation comprising 2,8-dimethyl-3-methylene-1-oxa-8-azaspiro[4,5]decane and adjust the molecular weight according to amount of release needed for the patients and to prolong the action of the compound on lacrimal and salivary glands, the

motivation would be the disclosure of Sako that PEO is the preferred polymer to achieve these results.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NABILA G. EBRAHIM whose telephone number is (571)272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/
Examiner, Art Unit 1618

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618